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(54) Title: PROCESS FOR SELECTIVE OXIDATION OF PRIMARY ALCOHOLS

(57) Abstract: The invention concerns a process for oxidising a primary alcohol such as a carbohydrate using an oxidising agent in the presence of a catalytic amount of a di-tertiary-alkyl nitroxyl, wherein the alcohol is oxidised using an oxidic compound of a period 4 or 5 metal having an oxidation state of a least +3 as an oxidising agent, for example manganese dioxide.

Process for selective oxidation of primary alcohols

[0001] The invention relates to the selective oxidation of primary alcohols, in a halogen-free process using an oxidising agent in the presence of a catalytic amount of a di-tertiary-alkyl nitroxyl compound, especially 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO).

[0002] Such a process is known from *Tetrahedron Lett.* 34, 1181-1184 (1993), which describes the oxidation of monosaccharides wherein the non-primary hydroxyl groups are partly protected, using sodium hypochlorite, potassium bromide and TEMPO in a two-phase solvent system (dichloromethane and water) to produce the corresponding uronic acid. WO 95/07303 describes a process for oxidising carbohydrates with hypochlorite/-TEMPO, using a pH of 9-13 in an aqueous medium. The oxidation of carboxymethyl and hydroxyethyl derivatives of starch and cellulose and other starch ethers with TEMPO is described in WO 96/38484.

[0003] These prior art oxidations have the advantage of being selective, in that oxidation of primary alcohol groups is strongly favoured over oxidation of secondary alcohol groups. However, the known processes use hypochlorite as the actual oxidising agent and thus produce chloride and some chlorinated byproducts; this is drawback as there is an increasing need for low-chlorine or even chlorine-free oxidation processes.

[0004] It was found now that the oxidation of primary alcohol functions can be carried out using inexpensive, without using equivalent amounts of chlorine compounds. The process of the invention allows to avoid the production of unwanted chlorine-containing oxidation products, especially in the case of oxidised carbohydrates. The process of the invention is characterised by using oxides and oxidic complexes of certain metals such as manganese, chromium, iron, nickel, ruthenium and vanadium. Examples include vanadium pentoxide, iron oxides, chromium trioxide and chromic acid salts, and especially manganese dioxide and permanganic acid salts. Especially manganese dioxide is a useful oxidising agent, as is it about 60% less expensive than hypochlorite (chlorine) on a molar basis. The process is defined by the features of the appending claims.

The metal oxides or oxidic metal complexes can be added as such to the reaction mixture. They can also be added on a solid support such as silicon dioxide or carbon black to facilitate their later separation from the reaction mixture. Another way of using the metal oxides is to produce them from metal species having lower oxidation states by oxidation with suitable oxidic reoxidant. Such reoxidants include hypochlorite (which can be washed off after the reoxidation), peroxides and organic and inorganic peracids. A very suitable

example is peroxosulphuric acid (Caro's acid) or a salt thereof. This is commercially available, e.g. under the trade name Oxone® of DuPont. In a particular embodiment, a low level of metal (e.g. divalent manganese or other) is used and is repeatedly or continuously oxidised in situ to the required metal oxide using the reoxidant; in this case a non-chlorine reoxidant such as a peracid or peroxide is advantageous. This mode of reaction is particularly advantage where inexpensive sources of the required transition metals are available. For example, manganese is usually present in wood fibres and therefore also in cellulosic pulp fibres, and it is also present at a level of about 0.1 % in technical magnesium oxide. A survey of manganese dioxide chemistry is given in Handbook of Reagents for Organic Synthesis; Oxidising and reducing agents, in particular p. 231 ff., Edited by Leo A. Paquette, John Wiley and Sons (New York).

[0005] Other means to improve the reaction is by the use of ultrasonic sound and of bromide as a catalyst in cases where (low) halogen contents are not a serious problem.

[0006] The amount of metal oxide to be used depends on the desired degree of oxidation of the product. When the metal oxides are used as such, typically 1.1 to 2.0 equivalents of metal oxides are used with respect to the desired degree of oxidation. When the metal oxides are generated in situ, lower levels can be used, e.g. 0.01 to 0.5 equivalents, in addition to e.g. 1.0 to 1.5 equivalents of reoxidant, such as peroxosulphuric acid.

[0007] In the following description, reference is made to TEMPO only for the sake of simplicity, but it should be understood that other di-tert-alkyl nitroxyls, such as 4,4-dimethyloxazolidine-N-oxyl (DOXYL), 2,2,5,5-tetramethylpyrrolidine-N-oxyl (PROXYL) and 4-hydroxy-TEMPO and esters and other derivatives and polymers thereof, and those described in WO 95/07303 can be substituted for TEMPO. 4-Hydroxy-TEMPO (which is preferably used at pH 4-5), 4-acetamido-TEMPO and dehydro-TEMPO (1,2,3,6-tetrahydro-2,2,6,6-tetramethylpyridin-1-oxyl) are advantageously used, as they are relatively easily accessible. The catalytic amount of nitroxyl is preferably 0.1-2.5% by weight, based on the primary alcohol, or 0.1-2.5 mol% with respect to the primary alcohol.

[0008] The process of the invention results in oxidation of primary alcohols initially to the corresponding aldehydes, and eventually to the corresponding carboxylic acids. In general, the second oxidation step, from aldehyde to carboxylic acid, proceeds at a faster rate than the first step, i.e. the oxidation from alcohol to aldehyde. The present process is especially favourable for the selective oxidation of primary hydroxyl groups in alcohols having a secondary alcohol function in addition to the primary alcohol, such as 1,6-octanediol, 1,9-octadecanediol, sugar alcohols, glycosides, and in particular carbohydrates having primary

alcohol functions such as glucans (starch, cellulose), furanofructans, galactans, (galacto)-mannans, and the like. A particular group of compounds suitable for oxidation with the present process are hydroxyalkylated, especially hydroxyethylated carbohydrates such as hydroxyethyl starch or hydroxyethyl inulin. These derivatives result in an alternative way
5 for producing formylmethyl and carboxymethyl carbohydrates.

[0009] The oxidation of carbohydrates containing primary hydroxyl groups results in the corresponding carbohydrates containing aldehydes and/or carboxylic acids with intact ring systems. Examples include α -1,4-glucan-6-aldehydes, β -2,1-fructan-6-aldehydes and β -2,6-fructan-1-aldehydes, with the corresponding carboxylic acids. Where these products still
10 contain the aldehydes, they have increased reactivity, e.g. in the case of cellulosic carbohydrates. Also, they are useful intermediates for functional carbohydrates wherein the aldehyde groups are further reacted with e.g. amine compounds and the like. They are also useful intermediates for crosslinked carbohydrates, in which the aldehyde groups are further reacted with e.g. diamine reagents. If the carboxylic acids are the desired oxidation
15 products, any residual aldehyde can be further oxidised to carboxylic acid using additional oxidising agent (e.g. manganese dioxide) or by conventional means, e.g. by using permanganate (optionally in the absence of TEMPO), chromate, hydrogen peroxide and catalyst, chlorite. Chlorite is also useful analytically, i.e. for checking the total degree of oxidation by converting all remaining aldehydes to uronic acid and comparing this with the
20 uronic acid content before chlorite oxidation.

[0010] The pH of the oxidation reaction can vary over a broad range, e.g. from about 1 to about 9. The pH can be used to influence the degree of oxidation, the higher degrees being obtained at lower pH values. Advantageously, a pH between 2 and 8, preferably between 3 and 6 and especially between 4 and 5 is used. The reaction temperature is preferably
25 between e.g. ambient temperature and 80°C, most preferably between 30 and 60°C. Spent oxidising agent, e.g. manganese oxides and salts, can be precipitated spontaneously or using e.g. alkali, collected by filtration and regenerated or discharged.

[0011] According to an advantageous embodiment of the invention, the primary oxidation step, i.e. the oxidation of the alcohol with TEMPO, can be separated from the secondary
30 oxidation step, i.e. the reoxidation of reduced TEMPO with the metal compound. This is especially useful where both the metal and the alcohol are insoluble, for example with manganese dioxide and cellulose pulps or cellulose-containing fibrous material. Thus, the oxidation of the alcohol (insoluble carbohydrate) can be performed a first reactor, the liquid effluent of the first reactor can be separated from the oxidised carbohydrate and be

introduced into a second reactor, where it is treated with the insoluble or immobilised metal compound, e.g. a manganese oxide bed. The metal compound can be filtered off and the filtrate can be recirculated to the first reactor. For example, a pulp is added to a liquor containing TEMPO, the oxidised pulp is filtered off, the TEMPO liquor is passed through a filter containing manganese dioxide and is thus reoxidised and recirculated. In this way, the process of the invention can also be performed in a semi-continuous or continuous mode.

Example 1

[0012] In 20 ml water 1.02 g of α -methylglucopyranoside (Aldrich, 99%) was dissolved. To this solution 10 mg of TEMPO, 1.1 g of manganese dioxide (Aldrich, 85%) and 1 ml of acetic acid (99%, Merck PA) were added. The solution had an initial pH between 2 and 3 and was heated in a closed flask to prevent loss of TEMPO due to evaporation) at 40°C during 60 hours. The black precipitate (probably a mixture of MnO and MnO₂) was removed by filtration and the uronic acid content was determined with the Blumenkrantz method (N. Blumenkrantz and G. Asboe-Hansen, *Anal. Biochem.* 54 484 (1973)) to be 55%.

Example 2

[0013] Example 1 was repeated with 0.510 g of methylglucopyranoside. The yield of uronic acid was 65%.

Example 3

[0014] Example 1 was repeated with 0.33 g of methylglucopyranoside. The yield of uronic acid was 60%. The filtrate was treated with 0.40 g of sodium chlorite to oxidise intermediate aldehyde groups. The initial pH of 4.6 started to decrease after a few minutes. A black precipitate formed and the solution turned yellow. After 2 hours, the uronic acid content was increased from 60% to 75%, and increases further after further reaction time.

Example 4

[0015] Example 1 was repeated, however using potassium permanganate (1 g in 200 mg portions) instead of manganese dioxide. The initial reaction occurred within 5 minutes (decoloration of the violet mixture and pH increase are visible within minutes). Also the formation of colloidal precipitate (probably a mixture of MnO and MnO₂) was observed, while manganese ions were found in solution. In the initial experiment a

conversion of 45 % to uronic acid was shown, and increased to 75 % after sodium chlorite (800 mg) treatment during one day.

Example 5

5 α -Methylglucopyranoside (0.52 g) was dissolved in 20 ml water and 1.0 g of manganese dioxide and 50 mg of 4-acetoxy-TEMPO were added. The mixture was shaken and allowed to react for 60 hours at 40°C. After filtration, sodium chlorite was added to the solution until no further pH change was observed (1 g was needed). The yield of uronic acid before reaction with chlorite was 23% and after this reaction it was 86%.

10 Example 6

In 100 ml of water 2.1 g of methyl- α -glucopyranoside, 100 mg 4-acetamido-TEMPO and 70 mg $\text{MnSO}_4 \cdot \text{H}_2\text{O}$ were dissolved. In the course of 8 hours small amounts (50-100 mg a time) of 6.3 g Oxone ($2\text{KHSO}_5 \cdot \text{KHSO}_4 \cdot \text{K}_2\text{SO}_4$, technical: 90% = 5.7 g pure = 9.3 mmol) were added. The pH was kept between 4 and 6 throughout the reaction. After 15 every addition of Oxone the pH decreased to about 3. By addition of 0.5M NaOH the pH was brought to >4. A dark brown precipitate was formed, which was present during the addition of Oxone. During reaction it was needed to add more NaOH because of acid formation (sulfuric and glucuronic acid). After one night of stirring the precipitate was dissolved. It appeared from the uronic acid assay (Blumenkrantz et al.) that after 20 hours of reaction 1.25 g (6.9 mmol) of glucuronic acid was formed. This corresponds to a yield of 75% (with respect to Oxone).

Example 7

In 100 ml of water 1.80 g of methyl- α -glucopyranoside, 80 mg 4-acetamido-TEMPO and 7 mg $\text{MnSO}_4 \cdot \text{H}_2\text{O}$ were dissolved. In the course of 2 hours small amounts (50-100 25 mg a time) of 3.1 g Oxone (2.8 g pure = 4.5 mmol) were added. The pH was kept throughout the reaction between 4 and 6. After every addition of Oxone the pH decreased to about 3. By addition of 0.5 M NaOH the pH was brought to 6 and kept at this value throughout the reaction. It appeared from the uronic acid assay (Blumenkrantz et al.) that 0.8 g of glucuronic acid was formed after 20 hours of 30 reaction. This corresponds to a yield of 90% (with respect to pure Oxone). Another 2.4 g of Oxone (2.2 g pure, 3.6 mmol) was added to the reaction mixture in the course of 3 hours. The total consumption of sodium hydroxide after completion of the reaction was

33 mmol. (pH 6). The yield of uronic acid was 7.5 mmol, which corresponds to approximately 92% conversion with respect to pure Oxone.

Claims

1. A process for oxidising a primary alcohol using an oxidising agent in the presence of a catalytic amount of a di-tertiary-alkyl nitroxyl, *characterised* in that the alcohol is oxidised using an oxidic compound of a period 4 or 5 metal having an oxidation state of at least +3 as an oxidising agent.
2. A process according to claim 1, in which the period 4 metal is selected from V^{5+} , Cr^{6+} , Mn^{4+} and Mn^{7+} .
3. A process according to claim 2, in which the oxidising agent is manganese dioxide or permanganic acid or a salt thereof.
4. A process according to anyone of claims 1-3, in which the primary alcohol is a carbohydrate, in particular starch or a starch derivative or cellulose.
5. A process according to any one of claims 1-4, which is carried out at a pH between 2 and 8.
6. A process according to any one of claims 1-5, in which said primary alcohol is a water-insoluble carbohydrate and the oxidation of the carbohydrate and the reoxidation of the nitroxyl compound are carried out in different reactors.
7. A process according to claim 6, which is carried out in a continuous mode.
8. A process according to any one of claims 1-7, in which the oxidic metal compound is produced by oxidation of a metal species in the presence of an oxidic reoxidant.
9. A process according to claim 8, in which the metal species is manganese and the reoxidant is peroxosulphuric acid.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/NL 00/00453

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C08B37/00 C08B31/18 C08B15/04 C07H1/00 C07H7/033
C07H3/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07H C08B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data, WPI Data, PAJ, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GB 670 928 A (CORN PRODUCTS REFINING COMPANY) 30 April 1952 (1952-04-30) claims ---	1-3
A	WO 99 23240 A (VALTION TEKNILLINEN TUTKIMUSKESKUS) 14 May 1999 (1999-05-14) abstract page 5, line 9 - line 14 ---	1,4,5
A	GB 570 364 A (STALEY MANUFACTURING CO) 4 July 1945 (1945-07-04) claims ---	1,2,4
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Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

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INTERNATIONAL SEARCH REPORT

International Application No

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	T.E. YEATES ET AL.: "Permanganate oxidation of corn starch" CEREAL CHEMISTRY, vol. 40, no. 6, 1963, pages 684-693, XP000863594 us abstract ---	1-4
A	CHEMICAL ABSTRACTS, vol. 130, no. 18, 3 May 1999 (1999-05-03) Columbus, Ohio, US; abstract no. 239099, "Manufacture of carboxyl containing polysaccharides by oxidation" XP002125009 abstract & JP 11 060602 A (MITSUBISHI GAS CHEMICAL CO. LTD) 2 March 1999 (1999-03-02) -----	1,2,4

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International Application No

PCT/NL 00/00453

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GB 570364	A		NONE		
JP 11060602	A	02-03-1999	NONE		